

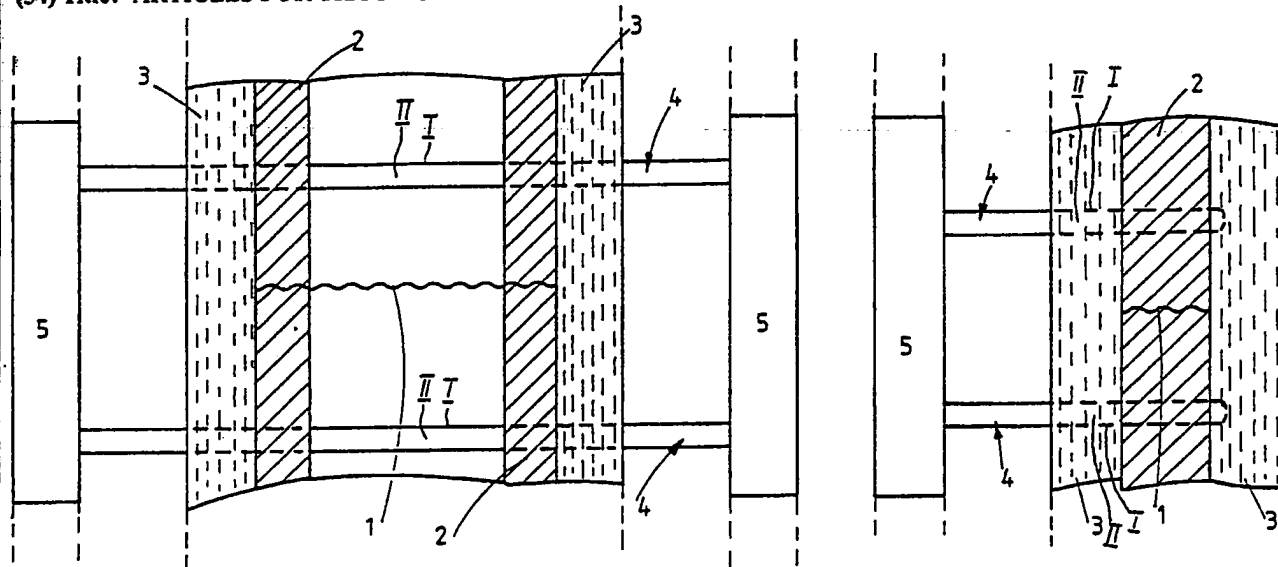


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**(54) Title:** ARTICLES FOR TISSUE CONTACT CONTAINING AN ANTIMICROBIAL AGENT



**(57) Abstract**

The invention relates to structures and/or devices which are in an intimate tissue contact or are installable at least partly to the inside of tissues and/or organs and/or body cavities (ducts), and which have some function (especially core layer II), such as the supporting and/or joining and/or replacing of tissues and/or organs or parts thereof, and/or the conveying of material and/or energy between various parts of the body and/or between the body and its environment. At least a part of the surfaces of the structures and/or devices in question comprises an organic and/or inorganic surface layer (I) containing antimicrobial or other chemotherapeutic substance or combination of substances being releasable from the surface layer in tissue conditions and preventing the growth of micro-organisms or corresponding organisms or killing them, thus preventing the propagation of micro-organisms and corresponding organisms, the start of infection, the propagation of infection, or suppressing infection, in the tissues and/or on the surface of the surface layer (I) of said structure and/or device.

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Articles for tissue contact containing an antimicrobial agent.

- 5 This invention relates to structures and devices for human and veterinary medicine, being defined more closely in the preamble of Claim 1.

10 In human and veterinary medicine a large number of different materials, implants, devices, components, tubes, catheters, sounds, fibres, fabrics etc. is used, which are in an intimate contact (a) with different tissues, such as skin, mucous membranes, interior parts of body cavities and/or of conduits  
15 (ducts) and/or (b) with operated and/or damaged tissues in such a way that they surround the tissues at least partly or they are at least partly located inside the tissues and/or the organs. In the text below, the above-mentioned materials, implants, devices, components, tubes, catheters, fibres, fabrics,  
20 etc., being in an intimate tissue contact and/or located at least partly inside the tissues and organs, are called jointly "structures and devices".

25 The "structures and devices" referred to above include e.g. douching tubes, kidney and urinary bladder catheters, conductors for electrical or hydraulic devices installed inside the body, pacemakers, materials and/or devices which are used for supporting  
30 and/or for replacing living tissues or parts thereof, such as artificial dura mater, fixation rings of heart valves, sutures, artificial joints and prostheses (e.g. hip joint and knee prostheses), implants which are used for replacing bone tissue or various

soft tissues (e.g. porous hydroxyapatite blocks and mammary prostheses), implants which are used for supporting and replacing tendons, ligaments and fasciae, devices which are used for internal and external fixation of bone fractures, ostoetomies, arthrodeses, damages in joints and cartilages, as well as other materials, devices, parts thereof or components which are intended for replacing, joining to each other, reforming or augmenting of tissues or parts thereof. Such materials, devices, their parts or components are manufactured usually of tissue-compatible materials, so called biomaterials. Typical known biomaterials include various tissue-compatible metals and alloys, ceramics and ceramic alloys, polymers, copolymers and polymeric alloys as well as various combination materials, i.e. composites, which are typically manufactured by combining material components having different properties (e.g. metals, ceramics, polymers).

Biomaterials can be biostable metals, ceramics, polymers, or mixtures or composites thereof. Biostable metals retain their properties in living tissues practically unchanged for long periods of time (typically at least several years). Biomaterials can be also either partially or totally biodegradable (degradable and/or soluble in tissue conditions) organic and/or inorganic materials, such as polymeric or ceramic materials. Biodegradable biomaterials and devices are described e.g. in inventions FI-851828 and EPO-146 398.

In the use of all the above-described materials and devices occurs always a certain number of disturbances or complications, which are caused by micro-organisms or organisms like micro-organisms and which

may prevent the material or device from appropriately serving its specific purpose.

Micro-organisms or organisms corresponding to micro-organisms can intrude into tissues in connection with human or veterinary medical use of the biomaterial, the device, or a part or a component thereof (called "structures or devices" below) e.g. in the following ways:

- 10 - By being conducted or growing along the surface or interior parts of the "structure or device" especially when part of the "structure or device" remains exposed outside the body,
  - By being released from the "structure or device" into the tissues, or
  - 15 - By transfer from the air of the operation room, from operation instruments, from textiles etc. into the operation wound.
- 20 Infections caused by micro-organisms or corresponding organisms can retard the healing of tissues, retard the fixation of the "structure or device" into tissues or in the worst case even lead to a situation where the infected "structure or device" and possibly
- 25 the tissues surrounding it as well must be removed from the body by means of a surgical operation. Problems of the above type are present e.g. in the use of sutures, tubes, catheters, conductors etc., i.e. in the use of "structures and devices" which pene-
- 30 trate the skin, the mucous membrane and other tissues from the outside of the body or the tissues or which have been at least partly positioned inside the body cavities or ducts in such a way that at least part of the "structure or device" is located outside the
- 35 body. In such a case micro-organisms or corresponding organisms can easily intrude deeper into the body

along the surface or interior parts of the "structure or device". Infection problems are also well-known in applications of such surgical implants like artificial joints and prostheses as well as replacement  
5 devices for bone tissue.

Surgical implants, such as artificial joints and prostheses, or other implants replacing or augmenting bone tissue, can be fixed into the body e.g. by means  
10 of bone cement or by constructing an open porous or fibrillar structure on the surface of the implants. The bony tissue or other tissue surrounding the implant inside the body can grow into said structure, thereby anchoring the implant fast in the tissue. The  
15 prior art includes e.g. open porous structures on the surface of metallic implants, said structures consisting of networks formed of metallic fibres, further, structures of polymeric fibres on the surface of an implant (e.g. CA-patent 1 141 293),  
20 or such structures with open porosity that are manufactured by sintering particles of metallic powder or ceramic powder on the surface of a macroscopic metallic sample, said particles forming a three-dimensional sponge-like structure on the sur-  
25 face of the implant. The above-described implants have typically a large external surface (especially in the case of implants with porous surface) forming a favourable base for attachment of micro-organisms, corresponding organisms, spores etc., and therefore  
30 for development of infection in the tissues surrounding the implant after the surgical operation.

The above-described problems can be decreased by means of hospital and operation room hygiene and  
35 sterility. However, even the best operation room technique can not eliminate the infection risk

totally. Further, the above-described problems can be reduced e.g. by treating the wound, operation instruments and/or the material, device, part or component thereof ( below "structures or devices") which will be located in the tissues, body cavity etc, with an antimicrobial substance or a mixture of substances (such as with antibiotics). Such a treatment can be carried out e.g. by rinsing the operation wound and/or the "structure and device" with a solution of an antimicrobial substance and/or by sprinkling a powder of an antimicrobial substance into the wound and/or onto the surfaces of the "structure or device". Such a local antimicrobial treatment (like sprinkling) has, however, a short-time effect, because the antibiotics or the like become dissolved in the tissue fluids and in the blood already during a few days at the most. Such a short time is not, as a rule, sufficient enough to destroy micro-organisms or the like effectively. If one wants to ensure a continuous effect of an antimicrobial agent by rinsing the wound and/or the "structure or device" continuously, a douching tube or tubes must be applied in order to conduct the antimicrobial liquid into the body and out of the body. Such a treatment is inconvenient for the patient and it can impede the nursing process as a whole. It is also possible to give antimicrobial agents in an injection or orally to the patient, but such a treatment, even if it is quite common, causes great physiological stress to the patient, because massive amounts of antimicrobial agent must be administered in order to increase its concentration to a value high enough in the infection area. It is also possible to implant biostable and/or biodegradable pearls, capsules, microcapsules etc. into the infected tissues. Such implants contain antimicrobial substance within a suitable carrier material (e.g. a

polymer), which releases the antimicrobial substance at a proper rate into its environment. Gentamycin-PMMA pearls (Septopal<sup>®</sup>) is an example of such devices. Such devices have, however, the drawback that they need a separate operation for their installation, and the operation can be difficult to carry out e.g. in a case of an infection extending deep into the tissues (e.g. an infection in connection of a joint prosthesis). In addition, pearls, capsules, microcapsules etc. form a separate foreign material phase in the tissue having no functional significance for the tissue in addition to the release of the antimicrobial substance. Therefore biostable pearls, capsules etc. must be removed in a separate operation after the infection is healed and/or the antimicrobial agent has been exhausted.

It is an object of the present invention to eliminate the disadvantages discussed above. The object is realised in a manner disclosed by the characterising portion of Claim 1.

It is an unexpected finding in connection with the present invention that tissue infections which occur in the use of "structures and devices", which are in an intimate tissue contact and/or are located at least partly inside the tissues and/or organs and/or body cavities (ducts), can be effectively reduced and prevented by using "structures and devices", whose surfaces are constructed at least partly of an organic or inorganic surface layer containing antimicrobial substance or other chemotherapeutical substance or combination of substances releasable in tissue conditions from the surface layer and preventing the growth of micro-organisms or corresponding organisms or killing them, thus preventing



the propagation of micro-organisms and corresponding organisms and the development and progress of infection in the tissues and/or on the surface of the surface layer in the structure and/or device, or  
5 suppressing the infection.

The surface layer can be typically located at least partly on the surface of a core layer (core material). The core material of the "structures and devices" of the invention can consist of a metal, metal  
10 alloy, ceramic, ceramic alloy, polymer, copolymer or polymer alloy or a composite consisting of different material components. Such "structures and devices" of the invention include e.g. artificial joints, prostheses, augmentation and replacement devices for bone  
15 tissue, internal and external fixation devices of bone fractures, osteotomies or arthrodeses, tubes, catheters, sounds, sutures, bands, cords, and other fibrous constructions.

20 It is characteristic of the surface layer that it releases antimicrobial substance or other corresponding chemotherapeutic substance into the surrounding tissues continuously at least for the time  
25 needed. Such a substance effectively prevents the development and progress of infection locally in the tissues, or it can suppress the infection already started.

Micro-organisms or corresponding organisms capable of causing the infection can intrude into the body in course of treatment, such as an operation, from the air or from the operation instruments or with the "structure or device" to be fixed or implanted into the body, or the micro-organisms can be conducted into the tissue by means of such a "structure or device" which partly remains exposed outside the body or inside a body cavity (duct) after the installation in place and/or the operation.

The antimicrobial substances or combinations of substances, being located in the surface layer of the "structure or device" and being releasable in tissue conditions, consist typically of some antibiotic, mixture of antibiotics, or some other chemotherapeutic compound or mixture.

The "structures or devices" according to the invention, or at least their surface layer or a part thereof can be constructed of organic material, such as wax-like or oligomeric materials, such as bone-wax, paraffin or the like corresponding materials, into which the antimicrobial substances can be dissolved or dispersed. The surface layer may also consist of a soluble polymeric material, such as for example polyethylene oxide or polypropylene oxide or their copolymer, polyvinyl alcohol or cellulose-polymer-derivatives etc. The "structures or devices" according to the invention or at least their surface layer may be constructed of biostable and/or biodegradable polymers as well. Tables 1 and 2 show some biostable and biodegradable and/or resorbable polymers suitable for the "structures or devices" according to the invention.

Table 1. Biostable polymers.

Name	Abbreviations
Polyethylenes	PE (LDPE, HDPE, LLDPE)
Polypropylene	PP
Styrene plastics	PS, ABS, SAN
Acrylonitrile-butadiene-styrene	ABS
Epoxy plastics	EP
Polyamides	PA6, PA66, PA11, PA12, PA64
Polyacetal	POM
Polyphenylene oxide	PPO
Polycarbonate	PC
Polymethylmethacrylate	PMMA
Polytetrafluorethylene	PTFE
Silicone polymers	SI
Polyurethanes	PU
Polyarylate	PAr
Polyarylsulphone	PAS
Polyetherketone	PEK
Polyetheretherketone	PEEK
Polyethersulphone	PES
Polyphenylene sulphide	PPS
Polyimide	PI
Polyamide-imide	PAI
Polyether-imide	PEI
Polysulphone	PSU
Thermoplastic fluoroplastics	ETFE, FEP, PFA, PVF
Thermoplastic liquid crystal polymers	LCP
Thermoplastic polyesters	PET, PBT

Table 2. Biodegradable and/or resorbable polymers.

Polymer	
Polyglycolide	(PGA)
Copolymers of glycolide:	
Glycolide/L-lactide copolymers	(PCG/PLLA)
Glycolide/tetramethylene carbonate copolymers	(PGA/TMC)
Poly lactides	(PLA)
Stereocopolymers of PLA:	
Poly-L-lactide	(PLLA)
Poly-DL-lactide	(PDLLA)
L-lactide/DL-lactide copolymers	
Copolymers of PLA:	
Lactide/tetramethylglycolide copol.	
Lactide/trimethylene carbonate copol.	
Lactide/ $\delta$ -valerolactone copol.	
Lactide/ $\epsilon$ -caprolactone copol.	
Polydepsipeptides	
PLA/polyethylene oxide copolymers	
Unsymmetrically 3,6-substituted poly-1,4-dioxane-2,5-diones	
Poly- $\beta$ -hydroxybutyrate	(PHBA)
PHBA/ $\beta$ -hydroxyvalerate copolymers	(PHBA/HVA)
Poly- $\beta$ -hydroxypropionate	(PHPA)
Poly-p-dioxanone	(PDS)
Poly- $\delta$ -valerolactone	
Poly- $\epsilon$ -caprolactone	
Methylmethacrylate-N-vinyl pyrrolidone copolymers	
Polyesteramides	
Polyesters of oxalic acid	
Polydihydropyrans	
Polyalkyl-2-cyanoacrylates	
Polyurethanes	(PU)
Polyvinylalcohol	(PVA)
Polypeptides	
Poly- $\beta$ -malic acid	(PMLA)
Poly- $\beta$ -alkanoic acids	
Polyvinylalcohol	(PVA)
Polyethyleneoxide	(PEO)
Ethyleneoxide-propyleneoxide copolymers	

Reference: S.Vainionpää, P.Rokkanen and P.Törmälä, Progr. Polym. Sci., in press.

In tissue conditions soluble inorganic materials, such as calciumsulphate (Plaster of Paris), water-glass, soluble calciumphosphate-glasses or other resorbable, tissue-compatible ceramic materials can be applied as materials for the "structures or devices" according to the invention or at least as their surface layers or as parts of the surface layers. As this kind of surface layer is resorbed (typically during a few days, weeks or months, depending on the chemical structure of the resorbable ceramic), it releases continuously antimicrobial substance into the surrounding tissues.

The "structure or device" of the invention can also consist of a biostable (metallic, ceramic, polymeric or compositic) core material, which is coated with an organic material containing at least antimicrobial substance, such as with a polymer, copolymer or polymer mixture or a low-molecular or oligomeric material, such as wax or the like, or with an inorganic material containing antimicrobial substance and being resorbable in tissue conditions, such as with gypsum, water-glass, or with other resorbable ceramics (which are disclosed e.g. in European Patent Application 146 398).

As a suitable surface layer and on the other hand a suitable antimicrobial substance is chosen, the concentration of the antimicrobial substance and the resorption rate from the device into the surroundings can be controlled within a wide range, for example from a few hours to an administration period of several months, using methods whose requirements are set by various specific practical applications.

The surface layer of the "structure or device" of the invention can also be constructed of a metallic and/or ceramic and/or polymeric layer having open porosity. The pores of such a layer may contain anti-  
5 microbial substance or the like chemotherapeutic substance and/or an admixture or an alloy of such materials and some above-mentioned resorbable or biodegradable organic or inorganic material (antimicrobial substance dissolved in the organic or  
10 inorganic material in question) as a filler. In this case, preferably

- (a) the degradation and/or the resorption of the organic or inorganic material,
  - (b) the release of the antimicrobial substance, and
  - 15 (c) the growth of cells from the surrounding tissues into the released open porosity (and possibly into the open porosity available already originally),
- all take place simultaneously. Consequently, the "structure or device" is firmly attached to the  
20 tissues.

It is self-evident, that the "structures and devices" of the invention, their surface layers and/or pores and possibly also the core materials can contain, in  
25 addition to an antimicrobial substance or a combination of substances, other additives as well, such as agents which accelerate the recovery of the tissues, agents which suppress the reaction against foreign material, antifungal substances, or other  
30 necessary additives.

The materials within the scope of the invention can be applied to the manufacture and use of a great variety of "structures and devices". Such "structures  
35 and devices" are typically represented by e.g.

- external and internal fixation devices for hard tissue and soft tissue surgery,
- various artificial joints, joint prostheses and tissue prostheses (such as joint prostheses, soft tissue prostheses, dental devices and prostheses and bone prostheses) ,or parts thereof,
- artificial bones and other bone prostheses,
- substitute materials for bone deficiency
- fibres, sutures, cords or strings, and the like structures made of fibres, such as artificial ligaments for joints and artificial tendons, and ligaments,
- tubes, douching tubes, catheters, permanent catheters, conductors and conduits and the like devices used in conducting materials (such as solutions, liquids, blood, plasma or the like), or energy (such as electric signals), between the tissues and/or body cavities, and/or into the tissues and/or into the body cavities from the outside of the body, and/or from the tissues and/or body cavities to the outside of the body, such as conduits for conveying liquids, wound drains, T-drains, blood vessel prostheses and tubes functioning as a reparation of ducts,
- tube-like, chute- or gutter-shaped structures, and the like support structures for joining broken and/or damaged nerves,
- substitutes for skin,
- heart valves, K-heart valves,
- temporary or permanent implants for fixation of damages of various tissues,
- devices for dentistry,
- tracheotomy tubes,
- pacemakers,
- electric conductors.

35

The invention and its additional advantages are ex-

plained more closely in the following description and examples, where reference is made to the embodiments shown by the accompanying drawings. In the drawings,

5 Fig. 1a is a schematic representation of an external fixation device for tibial fracture, shown in an installed state,

Fig. 1b is a schematic representation of an external  
10 fixation device for e.g. the wrist region, shown in an installed state,

Fig. 2 is a schematic representation of a spike in  
15 accordance with the invention in an external fixation device,

Fig. 3 is a representation of a hip joint prosthesis constructed in accordance with the invention,

20 Fig. 4 is a schematic perspective view of an implant which can be used e.g. for fixation of damages in a tubular bone, and

25 Fig. 5 is a representation of the fixation in accordance with Example 1.

The invention can be applied to external fixation  
30 devices for bone fractures e.g. in the following manner. The external fixation devices are formed of  
(a) fixation spikes, i.e. pins, which will be fixed onto the bone through the soft tissue, and  
(b) of support structures external of the body and  
35 serving as an attachment site for the spikes.

The known external fixation devices of this type are



schematically shown by Figs. 1a and 1b. Fig. 1a is a schematic longitudinal sectional view of a part of an external fixation device used e.g. in fixation of a tibial fracture 1. The device is formed of fixation spikes 4 passing through the tibia 2 and the soft tissue 3 surrounding it. The fixation spikes 4 are at their both ends fastened to the support structures 5 situated externally of the limb. The number of fixation spikes 4 is typically three on both sides of the fracture. Their number can vary, depending on the type of the fracture. Fig. 1b shows schematically an external fixation device for use e.g. in the wrist region. In this device the fixation spikes 4 pass through the soft tissues 3 only at their one ends and they are attached to a single support structure 5.

The greatest disadvantage in the surgical use of external fixation devices is the high percentage of infection. Typically approximately 4 to 30 % of operations lead to the start of an infection (viz. e.g. L.D.Anderson, W.C. Hudchins et.al., Clin.Orthop. 105:179, 1979; F.Bunny "Hoffman External Heart Frame Fixation: Current Concepts of External Fixation of Fractures", Springer-Verlag, Berlin, BRD, 1982).

The high percentage of infections is caused e.g. by the fact that the micro-organisms can invade the body from the outside via the fixation spikes through the skin wound present round the spike in the limb where the fixation has been made. It has been a surprising finding in connection with the present invention that as the fixation spikes 4, passing through the soft tissue and constituting the core layer II of the external fixation device, are coated (I) at least at their portions which will pass through the soft tissue with an organic or inorganic surface layer

containing antimicrobial substance or combination of substances releasable from the surface layer in tissue conditions, such as an antibiotic or a mixture of antibiotics, the percentage of infection in external fixation can be reduced significantly. The antimicrobial substance released from the surfaces of the spikes of the devices of the invention effectively prevents the transfer and propagation of micro-organisms from the wound present on the surface of the skin deeper into the tissues. The antimicrobial substance in question likewise effectively prevents the infective action of the micro-organisms situated in the implant or that of the microbes intruding the wound with the implant in course of the operation. The spikes of the external fixation devices in accordance with the invention may also have a porous surface structure, in which event they are formed e.g. of a metallic core material, coated with metallic filaments or fibres, or coated with a sintered metallic powder or ceramic powder. The open porosity in the surfaces of the spikes is in this case at least partly filled with in tissue conditions releasable antimicrobial substance or with some organic or inorganic material containing the antimicrobial substance, which will be released into the tissues. When using such devices, a strong anti-infective effect is obtained by virtue of the antimicrobial substance being delivered to the tissue. Fig. 2 shows schematically a fixation spike 4 (core layer designated II) in accordance with the invention, being coated with a coating 6 forming the surface layer I and containing antimicrobial substance. The spike 4 passes through the soft tissue 3 and the bone 2 to be fixed and is fastened to the external support structure 5.

The "structures and devices" according to the invention and of the above-described type can further be adapted to other surgical devices. One important field of application comprises artificial joints, such as knee joints, elbow joints, finger joints or hip-joint prostheses. Such artificial joints and prostheses or parts thereof may include parts which are suitably manufactured of layers from which the antimicrobial substance is released in tissue conditions. Fig. 3 shows schematically a hip-joint prosthesis in accordance with the invention (the core layer is designated at II). The prosthesis is constituted of a shaft portion 7, which is to be anchored in the core cavity of a cut femur, a neck 8, a spherical joint part 9, as well as a joint socket 10 (acetabulum), wherein the ball joint 9 is located. A tip portion 7a incorporated in the shaft portion and having a smooth surface in the case of Fig. 3 can be coated at least partly with an organic or inorganic surface layer I in accordance with the invention. The surface layer contains antimicrobial substance releasable in tissue conditions. Further, as seen in Fig. 3, a part of the surface of the shaft portion 7 (the upper part) and the outer surface of the joint socket 10 may have a structure which consists of material with open porosity in such a way that the open porosity has been effected by coating the shaft portion area in question with metallic filaments or fibres, or e.g. with sintered metallic or ceramic powder particles (surface layer I). In accordance with the invention, the porosity of the part of the implant containing the open porosity may be at least partly filled with an antimicrobial substance releasable in tissue conditions, or with a combination of an antimicrobial substance and some other organic or inorganic material. As a suitable

antimicrobial substance or a suitable mixture of an antimicrobial substance and a biodegradable or resorbable carrier material is used as the filler of the porous structure, the growth of bone tissue occurs preferably simultaneously into the porous structure of the shaft of the implant, while the antimicrobial substance and the optional biodegradable and/or resorbable admixture material is removed from the pores, eventually resulting in the growth of the bone tissue into the pores and consequently in the firm anchoring of the implant in the bone tissue, and the antimicrobial substance at the same time prevents tissue infections during its release, as the bone cells grow into the porous structure. A biodegradable or resorbable material combined with an antimicrobial substance is of particular advantage in "structures and devices" of the invention, because the biodegradation or resorption of the admixture material for its part sets the porous structures free and allows the bone tissue to fill the pores effectively in the surface structure of the shaft portion of the implant.

Fig. 4 shows a cylindrical implant in accordance with the invention, being constituted of a thicker middle portion 11 as well as of thinner cylindrical portions 12 attached thereto (core layer designated II). Because in this implant the end surfaces of the middle portion and the thinner cylindrical portions projecting therefrom (surface layer designated I) have surfaces provided at least partly with open porosity and the porous structure is at least partly filled with an antimicrobial substance or with a combination of an antimicrobial substance and an organic or inorganic material, in accordance with the

invention, such implants can be used effectively and safely e.g. as parts of a tubular bone on extending a tubular bone or on replacing a damaged bone or a chronically infected bone part with such an implant.

5  
According to one preferred embodiment, the surface layer I and the core layer II (material constituting the core) in the "structures and devices" of the invention are of the same material and also the core  
10 layer II may contain antimicrobial substance. Such "structures and devices" are e.g. biostable or biodegradable implants made entirely of a polymeric material or a polymeric composite, e.g. fixation  
15 screws, plates, rods, pins of external fixation devices, replacement devices for bone tissue, biostable joint prostheses, or parts or components thereof. These implants made of polymeric materials or of their composites can be provided with anti-  
20 microbial substances as early as during the polymerisation, during the processing of polymeric raw material to a half-fabricated product, or after the fabrication of the implant e.g. by absorbing the antimicrobial substance into the material. When such  
25 an implant is placed in the body, antimicrobial substance will be dissolved from the outer layer of the implant into the surrounding tissue, preventing infections effectively. The implants made of such material or a combination of materials can deliver  
30 antimicrobial substance in tissue conditions during a period of several months, provided that the concentration of the antimicrobial substance is sufficiently high in the surface layer and/or its diffusion from the surface layer into the surrounding  
35 tissues is slow enough, and/or the antimicrobial substance being diffused away from the surface into the tissues is continuously substituted by fresh

antimicrobial substance being diffused from the core material. As such polymeric implants of the invention are prepared of a biodegradable polymer, copolymer, mixture of polymers, or composite, they are particularly useful as fixation devices for bone fractures, osteotomies or arthrodeses, or as parts or components thereof, such as screws, rods, medullary nails, fixation plates or as fixation spikes of external fixation devices. The biodegradable implants of this type, made in accordance with the invention, support the tissues to be fixed for the required period, losing at the same time slowly their strength while the bone tissue is healing. The fixation devices deliver simultaneously antimicrobial substances into the bone tissue and/or the soft tissues surrounding them, which prevents infections effectively. After the the fracture has healed the biodegradable fixation devices or parts or components thereof do not need any operation for their removal, because the body uses the biodegradable implants as its nutrients. Consequently, e.g. when bone fractures, osteotomies or arthrodeses are fixed using the techniques of internal fixation, the patient will not be subjected to any kind of removal operation after the healing of the fracture. Further, as the biodegradable fixation spikes in accordance with the invention are used in the devices of external fixation, the fixation spikes inside the bone can be left at their places on removing the fixation device, because the body will use them as nutrients for its cells at a later stage.

The use of the at least partly biodegradable fixation devices according to the invention makes it also possible to eliminate complications from which the patient may suffer on removing a metallic fixation device, e.g. in case where a metallic screw, rod or pin is broken and remains partly embedded in the bone tissue.

Biostable or biodegradable fibres, monofilaments, sutures and other structures constructed of fibres, such as ribbons, cords and gauzes, containing antimicrobial substance or the like and being applicable to join or support various tissues, such as skin, muscles, ligaments, ligaments in joints, fasciae, inner organs, etc., as well as to close wounds, go under the concept "structures and devices" of the invention. The above-mentioned structures have at least in their surface layers antimicrobial substance being releasable in tissue conditions. Sutures or the like structures constructed of biodegradable fibres constitute a particularly advantageous embodiment. They support the tissues to be joined for the period required, delivering at the same time antimicrobial substance into the surrounding tissue and they will eventually disappear through the metabolic activity of the cells after they have completed their function.

The "structures and devices" of the invention encompass also tubes, such as douching tubes, blood vessel catheters, kidney and urine bladder catheters, and the like structures being made of a biostable and/or biodegradable polymer, copolymer or mixture of polymers and containing in tissue conditions releasable

antimicrobial substance at least in their surface layers. These structures are used for conducting among other things plasma, blood, solutions, or the like liquids into the body to the tissues or body cavities, or for conducting liquids or the like out of the tissues or from body cavities, or for conducting liquids or the like between the tissues and/or organs and/or body cavities. Such tubes or corresponding structures, releasing antimicrobial substance to their surroundings, stop effectively the propagation of micro-organisms or the like from the outside of the body into the tissues or between the tissues.

15 In accordance with a preferred embodiment, the "structures and/or devices" in accordance with the invention may also contain one or several cavities or the like, which are substantially filled with an antimicrobial substance or mixture of substances, being releasable in tissue conditions. This makes it possible to raise the total amount of the antimicrobial substance inside the "structure or device" to a high value. When the antimicrobial substance is diffused from the "structure or device" via its outer surface to the surrounding tissues, fresh substance will be so diffused from the cavity/cavities, substituting the substance diffused away, that the concentration of the antimicrobial substance in the "structure and/or device", in its surface layer I, and consequently in the surrounding tissue as well, will remain high for a long period of time. The communication of the cavity with the surface layer can be closed with a material that is at least partly biodegradable in tissue conditions and/or is resorbed rapidly, in which event the communication with the surface layer will be opened.



The invention will be illustrated by means of the following examples.

5     **Example 1.**

A fixation device of the type shown in Fig. 1b and constructed for research purposes was used. The device was constituted of an external support structure and of fixation spikes (so-called "half-pins"), which  
10     were supported by the structure and were to be fastened into a bone. The device was used for the external fixation of a distal femoral osteotomy of a rabbit in the following manner.

15     The steel spikes (thickness 1.6 mm) in the fixation devices for the test group (20 rabbits) were coated at the portions which would pass through the soft tissues, and at the length of 10 mm at the portions  
20     which would remain outside the tissues, with a layer of poly-DL-lactide (MW 100 000), having a thickness of 0.3 mm and containing as an admixture 10 wt-% of Cephalosporine dissolved therein.

25     The devices for the control group (20 rabbits) were left uncoated.

All fixation devices were sterilised with ethylene oxide.

30     The hairs in the region of the distal lateral side in the femur of an anaesthetised rabbit were shaved off, the skin was washed with a solution "Neo-Amisept" and the distal part of the femur was exposed with a longitudinal cut. On the distal side of the planned os-  
35

teotomy plane two small skin cuts were made, into which the fixation spikes were inserted to a bone contact, whereafter the spikes threaded at their tip portions were so screwed into the bone that they  
5 pierced both cortexes. Similar operation was done on the proximal side of the osteotomy plane by using three fixation spikes. The fixation spikes were fastened onto the support structure.

10 Osteotomy was carried out in the femur with a diamond wheel at the height of approximately 2 cm up from the knee joint at the region of spongiosa bone. The bone surfaces were brought into a compression contact by adjusting at the support structure the mutual distance of the proximal and distal spike groups. The  
15 wound was closed with a biodegradable suture (fixation shown schematically in Fig. 5).

The control group, whose fixation spikes were left  
20 uncoated, exhibited 4 infections at the region of the fixation spikes in the tissues during healing. The test group employing the spikes coated with the polylactide-antibiotic-admixture exhibited during healing only one superficial infection at the region of a  
25 spike piercing the skin.

#### Example 2.

30 Catheter tube having an outer diameter of 1 mm and an inner diameter of 0.7 mm was prepared by extrusion from polydimethylsiloxane (MW 120 000) containing 6 wt-% of Cephalosporine. A tube without Cephalosporine was prepared as well. The catheters were sterilised  
35 with ethylene oxide.

The hairs in the abdominal region of an anesthetised rabbit were shaved off, the skin was washed with a solution "Neo-Amisept", and the abdominal cavity was opened by making a lower median cut. The peritoneum was not opened, but the peritoneal organs were moved together with the peritoneum upwards and the operation was continued in the true pelvis (pelvis minor) as far as the urine bladder, which was opened. Two small-diameter catheters were introduced via the urethra into the bladder, and one of them was led to the right urine duct (ureter) and the other was led to the left one, and they were pushed close to the renal pelvis (pelvis renalis). The bladder as well as the lower median cut wound were closed with biodegradable sutures. Ten rabbits had catheters made of the antibiotic-polymer-admixture and ten rabbits had the same made of the bare polymer. The samples for bacterial incubation of the urine were taken on 1st, 3rd, 7th, 14th and 21th days after the operation. After one week from the operation, the group having the antibiotic-polymer-admixture tubes had two cases of bacterial growth of magnitude  $10^6$ , (being a sign of a clear inflammation in the lower urinary system) and the group having the bare polymeric tubes had six cases of this type.

### Example 3

The hairs in the hip region of an anesthetised rabbit were shaved off and the soft tissues were opened in the region of the greater trochanter (trochanter major) in the upper part of the femur. The greater trochanter was exposed, a passage extending to the core cavity was made by drilling with a rose bit and the passage was expanded with a core rasp. In the

core cavity of the femur, a cylinder made of Co-Cr-Mo-alloy (ASTM F-75) was installed. The cylinder had a length of 4 cm and it was coated with a porous metallic coating of the type Porocoat<sup>®</sup> along one half  
5 of its length (coating: a sintered Co-Cr-Mo-powder; thickness 3/4 mm, degree of porosity 40%, medium pore size 250 µm; viz. e.g. T.S.Smith, 30th national SAMPE Symposium, March 19-21, 1985, pp. 222-229).

10 The test group (30 rabbits) had implants where the pores in the porous region were according to the invention filled (by using hot-melt technique) with a mixture, which consisted of 93 wt-% of polyglycolide (MW 40 000) and of 7 wt-% of antibiotic Ciprobay<sup>®</sup>  
15 200. The control group (30 rabbits) had implants with no polymer-antibiotic-coating in the porous region.

The wound was closed layer by layer with resorbable sutures. Observing times were 1, 3, 6 and 24 weeks.  
20 After the sacrifice of the animal, the concentration of the antibiotic after 1 and 3 weeks in the bony tissue of the porous region of the implants in accordance with the invention was determined. The concentration was in all cases equal to a value superior  
25 to 2 MIC and thus it was high enough to destroy Streptococcus and Staphylococcus germs, which are the most frequent bacteria that cause inflammation in connection with artificial hip joint operations. No deep infections were present in the test group. The  
30 control group exhibited one deep infection.

After 24 weeks the growth of the bone tissue had significantly filled the volume of the pores both in the test group and in the control group. The test  
35 group showed no more any traces of biodegraded polyglycolide and of antibiotic either.

## Example 4

The pores of the cylinders in accordance with Example 3 having partly a porous surface were filled with an admixture of a biodegradable ceramic powder (average particle size 1  $\mu\text{m}$ ) and/or a biodegradable polymeric powder (average particle size 1  $\mu\text{m}$ ) and Ciprobay<sup>®</sup> 200 by melting the polymeric phase and by pressing the admixture of the polymeric melt, the ceramic powder and the antibiotic into the pores with the aid of vacuum and overpressure. Table 3 shows the used admixtures of materials.

Table 3. Admixtures of materials used for filling the pores in the cylindrical implants.

No.	Ceramic powder	Percentage of ceramic powder (wt-%)	Polymer	Percentage of polymer (wt-%)	Percentage of Ciprobay <sup>®</sup> 200 (wt-%)
1.	Calcium metaphosphate	40	Polyglycolide (MW 40 000)	55	5
2.	Calcium metaphosphate	35	Poly-DL-lactide (MW 60 000)	58	7
3.	CaSO <sub>4</sub>	30	Glycolide/lactide copolymer (85/15, MW 60 000)	64	6
4.	Calcium metaphosphate	93	-	-	7

The implants treated with the materials of Table 3 were implanted into the core cavities of the femurs of rabbits (10 rabbits per material) using the technique described in Example 3. The determination of the antibiotic concentration in the bone tissue of the porous region after 1 and 2 weeks resulted in all cases in values corresponding to a value superior to 2 MIC.

In the case of the control group (10 rabbits) the porous implants were dipped in a commercial Ciprobay<sup>®</sup> 200 solution before the implantation. The determination of the antibiotic concentration in the bony tissue of the porous region after two weeks gave a negative result in all cases.

The histological test after 8 months from the implantation showed that the biodegradable ceramics and polymers had biodegraded completely and had been replaced with fresh bone.

#### Example 5

The fixation devices of Fig. 1a were prepared by using carbon fibre reinforced (parallel fibre reinforcement) polyamide-66 (PA66) rods having a diameter of 2.5 mm as the fixation rods. The rods contained Gentamycin sulphate, corresponding to 4 wt-% of Gentamycin, in their polymeric matrixes as a homogenic molecular mixture. The amount of carbon fibres was 30 wt-%. In addition, rods were coated with a 0.3 mm thick layer of PA66-Gentamycin-admixture (mixing ratio 94/6). The rods were fixed, following the principle in Fig. 1a, on both sides to a support structure of steel.

The fixation devices were used for fixation of the proximal spongiosa region in a rabbit femur by drilling on both sides of the osteotomy two drill holes, through which the fixation rods were hammered and the fixation rods were affixed on both sides to support structures of steel. The corresponding tests were conducted with the fixation rods of the same type without Gentamycin. The Gentamycin group (20 rabbits) had 40% less of infections than the control group (20 rabbits, no Gentamycin).

#### Example 6.

The open porosity of porous hydroxyapatite (HA) blocks (Interpore 200 <sup>TM</sup>) was filled with a melt of an admixture of polyglycolide (PGA) (MW 40 000) and Ciprobay<sup>®</sup> 200 (PGA/antibiotic ratio 92/8 w/w) using vacuum technique. The chilled blocks were sawed into cubes (dimensions ca. 4x4x4 mm). The infected bone tissue was removed from 6 rabbits having an induced chronic osteomyelitis in the distal spongiosa bone region in the femur, and the removed bone tissue was replaced with the HA-PGA-antibiotic-blocks of the invention. After the observation of 6 months the infections had ceased exclusive one rabbit, and the histological test showed that in the case of 5 healed rabbits the PGA-antibiotic-mixture had biodegraded and the HA-blocks had been filled with fresh bone.

#### Example 7.

Polyglycolide sutures (Dexon<sup>®</sup>, size 2 USP) were coated with a Ciprobay<sup>®</sup> 200 antibiotic by dipping the

sutures in the antibiotic solution and by subsequent drying. The coating was repeated until the antibiotic consisted of 2.5 wt-% of the weight of the threads.

- 5 The sutures treated with antibiotic were heated in a pressurised (surface pressure of 200 MPa) mould having the shape of a screw (length of the screw cavity 50 mm, maximum width of the screw thread 4.3 mm and minimum width 3.2 mm, diameter of the screw head 8 mm) at a temperature of 218°C in a nitrogen atmosphere for a period of 5 min., during which process the partly softened fibrous material was sintered together. The mould was rapidly chilled to room temperature. The bending strength of the self-reinforced, antibiotic containing biodegradable screws so prepared was 160 MPa.

The screws having the antibiotic concentration were used for the fixation of the osteotomy made in the spongiosa bone region of the lower part of the rabbit femur by drilling a drill hole through the plane of osteotomy, by threading the drill hole and by screwing and tightening the screw into the drill hole.

- 25 A Staphylococcus-infection was induced artificially in the operation wound. In the test group of 20 rabbits, 16 osteotomies healed normally and 4 had a retardation of bone formation caused by the infection. The number of the retardations of the bone formation, caused by the infection, was 12 in the control group (20 rabbits) having the corresponding biodegradable self-reinforced screws without the antibiotic.



Example 8.

Monofilaments were prepared from a mixture of polyglycolide (MW 40 000) and Ciprobay<sup>®</sup> 200 (weight ratio 5 .98/2) by extrusion. The thickness of the monofilaments was ca. 15 µm and they were twisted into sutures (size 2 USP). The polyfilament sutures so obtained were sterilised in a normal ethylene oxide sterilisation. The antibiotic containing sutures so 10 prepared were used for the closure of a longitudinal cut made in the abdominal region of a rabbit by using a layer-by-layer closing technique. Two rabbits (5%) in the test group of 40 rabbits exhibited sinus formation, which apparently was at least partly caused by 15 bacteria.

The number of sinus cases was three (7.5 %) in the control group with the corresponding polyglycolide sutures prepared without the addition of an anti- 20 biotic.

Claims:

5 1. Structures and/or devices for an intimate tissue  
contact and/or for installation at least partly to  
the inside of tissues and/or organs and/or body  
cavities (ducts), having some function, such as the  
supporting and/or joining and/or replacing of tissues  
10 and/or organs or parts thereof, and/or the conveying  
of material and/or energy between various parts of  
the body and/or between the body and its environment,  
characterised in that at least part of the surfaces  
of said structures and/or devices comprises an  
15 organic and/or inorganic surface layer (I), which  
contains antimicrobial or other chemotherapeutic  
substance or combination of substances being re-  
leasable from the surface layer in tissue conditions  
and preventing the growth of micro-organisms or  
20 corresponding organisms or killing them, thus pre-  
venting the propagation of micro-organisms or cor-  
responding organisms, the starting of infection, the  
propagation of infection, or suppressing the latter,  
in the tissues and/or on the surface of the surface  
25 layer (I) of the structure and/or device.

2. Structures and/or devices as claimed in Claim 1,  
characterised in that at least their surface layer  
comprises open porosity.

30

3. Structures and/or devices as claimed in Claim 1  
and/or claim 2, characterised in that they comprise a  
core layer (II) having a composition similar to that  
of said surface layer (I).

4. Structures and/or devices as claimed in Claims 1 to 3, characterised in that at least part of the surface layer (I) consists of a biodegradable or resorbable polymer, copolymer or mixture of polymers.

5

5. Structures and/or devices as claimed in Claims 1 to 4, characterised in that at least part of the surface layer (I) consists of a resorbable ceramic material.

10

6. Structures and/or devices as claimed in Claims 1 to 5, characterised in that the surface layer (I) at least partly consists of a porous or fibrous material, wherein the pores or the spaces between the fibrous structural units are at least partly filled with an organic or inorganic material containing antimicrobial or other chemotherapeutic substance being releasable at least in tissue conditions.

15

20

7. Structures and/or devices as claimed in Claims 1 to 6, characterised in that they comprise at least a core layer (II) made of metal, metal alloy, ceramic or polymeric material, mixture of ceramics and/or polymers, or any combination material of the above-mentioned materials, i.e. composite, the structures and/or devices further comprising an organic or inorganic surface layer (I) covering at least partly the core material and containing antimicrobial substance or combination of substances being releasable in tissue conditions.

30

8. Structures and/or devices as claimed in Claims 1 to 7, characterised in that the surface layer (I) is at least partly formed of metal, metal alloy, ceramic material or polymeric material, mixture of ceramics

35

and/or polymers, or any composite of the above-mentioned materials.

5 9. Structures and/or devices as claimed in Claims 1 to 8, characterised in that the pores of the surface layer (I) at least partly contain organic and/or inorganic material, which at least partly is formed of an antimicrobial substance or combination of  
10 substances being releasable in tissue conditions, and optionally of an admixture material which may be at least partly biodegradable and/or resorbable.

10. Fibres, monofilaments, sutures and other  
15 structures and devices constructed of fibres, and intended for supporting and/or joining of tissues and for closing wounds, as claimed in Claims 1 to 9.

11. Surgical implant materials and surgical im-  
20 plants, which at least partly can be manufactured therefrom, such as artificial joints and prostheses, augmentation and replacement devices for bone tissue, bone-graft powders, devices for use for internal and external fixation of bone fractures, and/or parts  
25 and/or components of the above-mentioned implants or devices, as claimed in Claims 1 to 9.

12. Tubes, such as douching and drain tubes, kidney and urine bladder catheters, and corresponding struc-  
30 tures for conveying among other things solutions and other liquids to the inside of the body into tissues or into body cavities, or liquids and corresponding material out of tissues or body cavities, or for conveying liquids or the like between tissues and/or  
35 organs and/or body cavities, as claimed in Claims 1 to 9.

13. Structures and/or devices as claimed in Claim 12, characterised in that they pass through the skin in such a manner that at least part of the implant is situated outside the tissues and/or that they are  
5 situated at least partly within body cavities or blood vessels or ducts.

14. Structures and/or devices as claimed in Claims 1 to 9, characterised in that they contain at least one  
10 cavity or the like, in particular situated within the core layer (II) and containing antimicrobial or other chemotherapeutic substance or combination of substances being releasable in tissue conditions, and that said at least one cavity is arranged to com-  
15 municate with the surface layer (I) at least in tissue conditions.

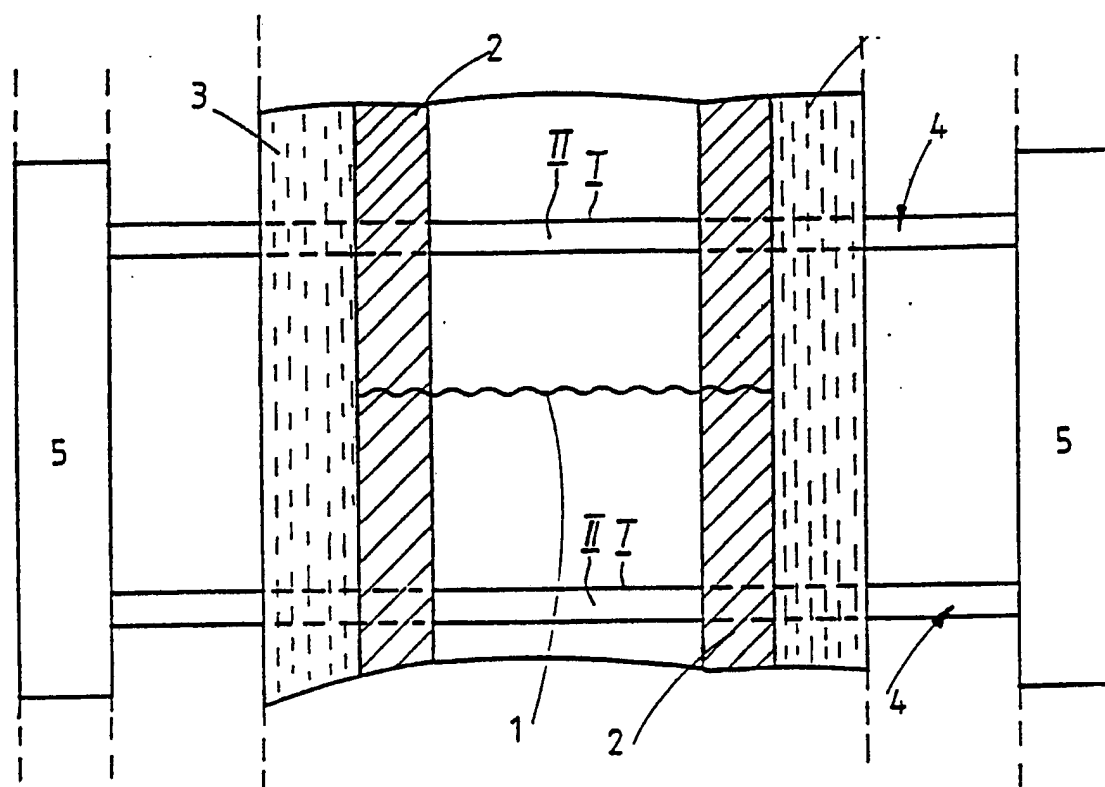


Fig 1a

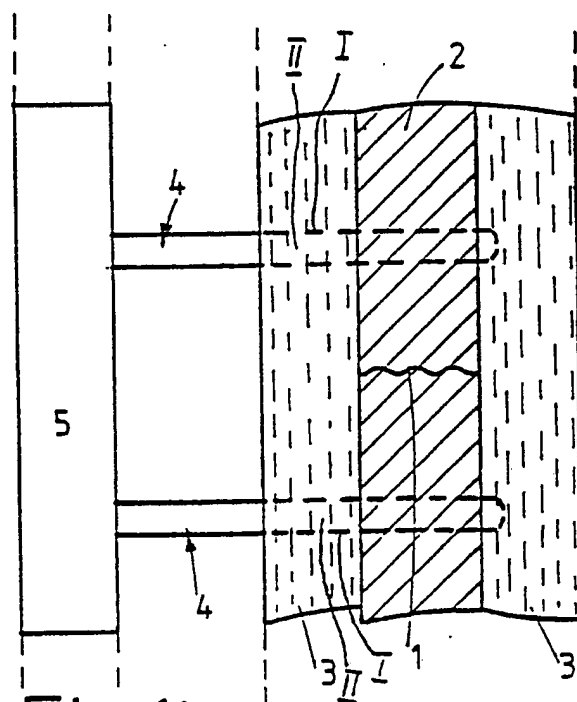


Fig 1b

Fig 2

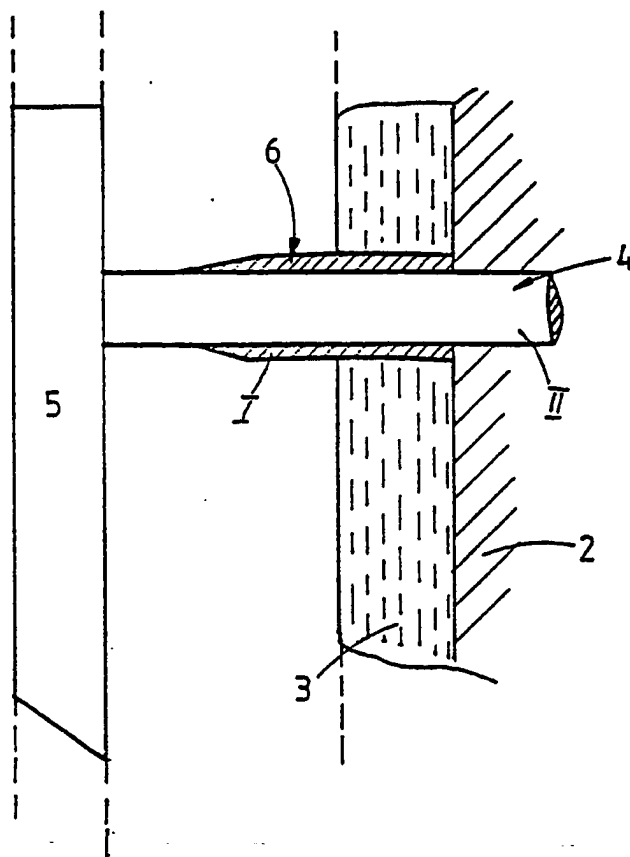


Fig 3

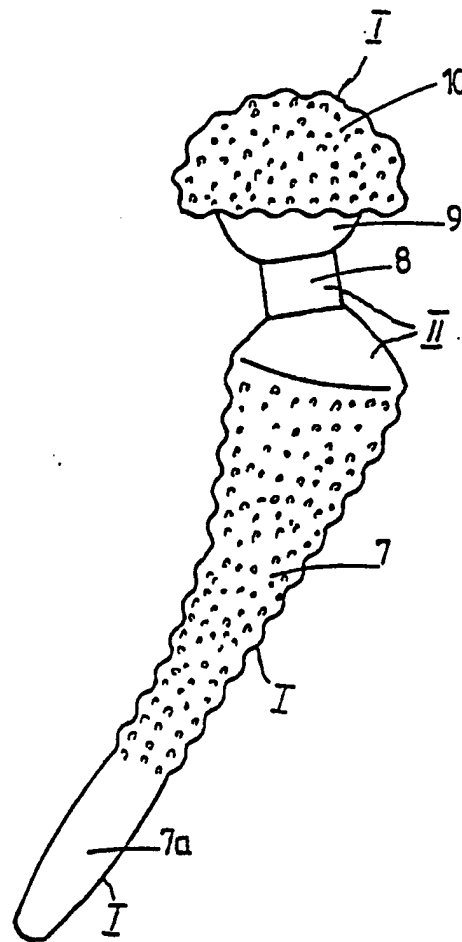


Fig 4

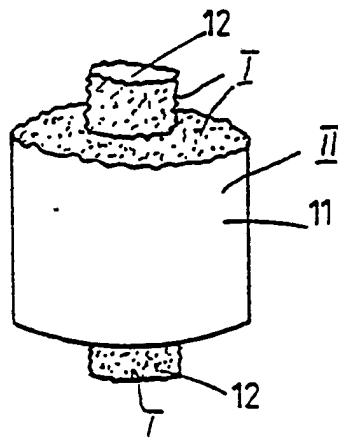
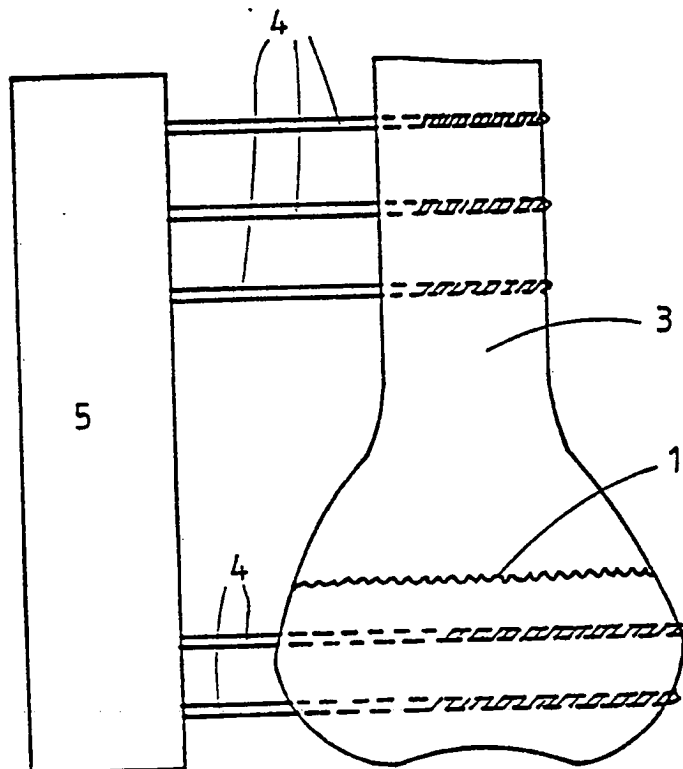




Fig 5



# INTERNATIONAL SEARCH REPORT

International Application No PCT/FI88/00191

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <sub>4</sub> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">A 61 L 27/00</div>																	
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; font-size: 0.8em;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> <div style="font-size: 0.8em;">Classification System  </div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">IPC 4</div> </td> <td style="width: 50%; border: none; vertical-align: top;"> <div style="font-size: 0.8em;">Classification Symbols</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">A 61 F; A 61 L</div> </td> </tr> </table> <div style="text-align: center; font-size: 0.8em; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched <sup>8</sup></div> <div style="text-align: center; font-family: monospace; font-size: 1.2em; margin-top: 10px;">SE, NO, DK, FI classes as above.</div>			<div style="font-size: 0.8em;">Classification System  </div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">IPC 4</div>	<div style="font-size: 0.8em;">Classification Symbols</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">A 61 F; A 61 L</div>													
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<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; font-size: 0.8em;">Category <sup>10</sup></th> <th style="width: 70%; font-size: 0.8em;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 20%; font-size: 0.8em;">Relevant to Claim No. <sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">           US, A, 4 610 692 (JURGEN EITENMULLER et al)                              9 September 1986                      &amp; EP, 0058867                          DE, 3106445                          CA, 1195615                          DE, 3126273                          DE, 3133015                          DE, 3133016         </td> <td style="text-align: center; vertical-align: top;">1-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">           US, A, 3 987 797 (MARTIN STEPHENSON)                              26 October 1976                      &amp; DE, 2555624                          JP, 52070587         </td> <td style="text-align: center; vertical-align: top;">1-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">           US, A, 3 991 766 (EDWARD SCHMITT et al)                              16 November 1976                      &amp; US, 3875937         </td> <td style="text-align: center; vertical-align: top;">1-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">           US, A, 3 896 812 (KEONARD D. KURTZ)                              29 July 1975                      &amp; FR, 1583560                          GB, 1229425                          GB, 1241288  <div style="text-align: right; font-size: 0.8em;">.../...</div> </td> <td style="text-align: center; vertical-align: top;">1-14</td> </tr> </tbody> </table> <div style="font-size: 0.8em; margin-top: 10px;"> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents: 10</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Z" document member of the same patent family</p> </div> </div> </div>			Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	X	US, A, 4 610 692 (JURGEN EITENMULLER et al) 9 September 1986 & EP, 0058867 DE, 3106445 CA, 1195615 DE, 3126273 DE, 3133015 DE, 3133016	1-14	X	US, A, 3 987 797 (MARTIN STEPHENSON) 26 October 1976 & DE, 2555624 JP, 52070587	1-14	X	US, A, 3 991 766 (EDWARD SCHMITT et al) 16 November 1976 & US, 3875937	1-14	X	US, A, 3 896 812 (KEONARD D. KURTZ) 29 July 1975 & FR, 1583560 GB, 1229425 GB, 1241288 <div style="text-align: right; font-size: 0.8em;">.../...</div>	1-14
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X	US, A, 3 896 812 (KEONARD D. KURTZ) 29 July 1975 & FR, 1583560 GB, 1229425 GB, 1241288 <div style="text-align: right; font-size: 0.8em;">.../...</div>	1-14															
<b>IV. CERTIFICATION</b> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> <div style="font-size: 0.8em;">Date of the Actual Completion of the International Search</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">1989-02-07</div> </td> <td style="width: 50%; border: none; vertical-align: top;"> <div style="font-size: 0.8em;">Date of Mailing of this International Search Report</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">1989 -03- 0 1</div> </td> </tr> <tr> <td style="width: 50%; border: none; vertical-align: top;"> <div style="font-size: 0.8em;">International Searching Authority</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">Swedish Patent Office</div> </td> <td style="width: 50%; border: none; vertical-align: top;"> <div style="font-size: 0.8em;">Signature of Authorized Officer</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">Hans-Christer Jönsson</div> </td> </tr> </table>			<div style="font-size: 0.8em;">Date of the Actual Completion of the International Search</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">1989-02-07</div>	<div style="font-size: 0.8em;">Date of Mailing of this International Search Report</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">1989 -03- 0 1</div>	<div style="font-size: 0.8em;">International Searching Authority</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">Swedish Patent Office</div>	<div style="font-size: 0.8em;">Signature of Authorized Officer</div> <div style="text-align: center; font-family: monospace; font-size: 1.2em;">Hans-Christer Jönsson</div>											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	DE, 1767484 FR, 2181633 CA, 955175 GB, 1398127 CH, 575763 JP, 49021990	
X	EP, A1, 0 022 289 (THE PROCTER & GAMBLE COMPANY) 14 January 1981 & JP, 56045954 US, 4343788 CA, 1156932 US, 4479795	1-14
X	DE, A1, 3 503 126 (MEADOX MEDICALS INC.) 1 August 1985 & BE, 901611 FR, 2558720 GB, 2153235 NL, 8500239 SE, 8500422 JP, 61092672 GB, 2187191 GB, 2187192 AU, 575617	1-14
X	Dialog Information Services, File 351, World Patent Index 81-89, Dialog accession no. 2953602, Mosc Med Inst: "Human blood vessel prosthesis contg. synthetic fabric sleeve, sleeve lined with collagen film and coated with collagen sponge contg. drugs", SU 904693, A, 820215, 8249 (Basic)	1-14
X	EP, A1, 0 141 628 (UNITIKA LTD.) 15 May 1985 & JP, 60094460 US, 4675347 JP, 60096258	1-14
X	WO, A1, 86/02561 (BROHULT JOHAN) 9 May 1986 & SE, 8405504 EP, 0199792	1-14
X	GB, A, 2 190 387 (YARSLEY TECHNICAL CENTRE LIMITED) 18 November 1987	1-14
X	US, A, 4 615 705 (JOHN T. SCALES et al) 7 October 1986 .../...	1-14

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	GB, 2072514 GB, 2073024 WO, 81/02667 WO, 81/02668 EP, 0048246 EP, 0048247 US, 4476590	